

=> s glycine transport inhibitor?

140522 GLYCINE

651695 TRANSPORT

931041 INHIBITOR?

L1 40 GLYCINE TRANSPORT INHIBITOR?
(GLYCINE(W) TRANSPORT(W) INHIBITOR?)

=> s alzheimers

L2 2719 ALZHEIMERS

=> s l1 and l2

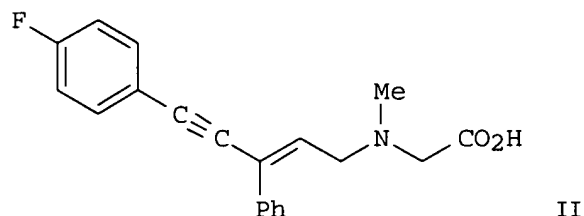
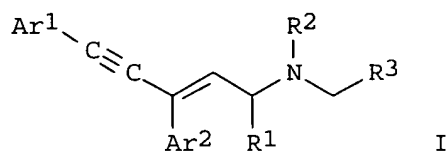
L3 1 L1 AND L2

=> d cbib abs

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN

2002:570709 Document No. 137:124979 Preparation of diaryl-enyne glycine derivatives as **glycine transport inhibitors** for treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease. Egle, Ian; Frey, Jennifer; Isaac, Methvin (NPS Allelix Corp., Can.). U.S. US 6426364 B1 20020730, 19 pp. (English). CODEN: USXXAM. APPLICATION: US 2000-704225 20001101. PRIORITY: US 1999-PV162986 19991101.

GI



AB Title compds. I [wherein Ar1 and Ar2 = independently (un)substituted (hetero)aryl; R1 = H or alkyl; R2 = H, alkyl, or benzyl; R3 = CO2R, CONRR', CONH(OH), COSR, SO2NRR', PO(OR)(OR'), or tetrazolyl; R and R' = independently H or alkyl; and salts, solvates, or hydrates thereof] were prepared in several steps from aryl iodides, alkynes, and sarcosines. For example, Me phenylpropiolate was coupled with TMSCH₂CH₂CH₂ in the presence of Pd(OAc)₂ and tris(2,6-dimethoxyphenyl)phosphine to give 1-methoxycarbonyl-2-phenyl-4-trimethylsilyl-1-buten-3-yne (86%), which was reduced to the alc. using DIBAL-H (71%). Bromination, followed by addition of t-Bu sarcosine•HCl, afforded the tertiary amine (58% over 2 steps). Desilylation with K₂CO₃ in MeOH (99%), arylation with 4-fluoriodobenzene in the presence of Pd(PPh₃)₄, CuI, and NEt₃ (77%), and deesterification with HCO₂H (90%) gave the pentenyne II. I are active as GlyT-1 inhibitors and bind to the glycine sites on the NMDA receptor (no data). Thus, I are useful for the treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease (no data).

=> s glycine

L4 140522 GLYCINE

=> s l4 and l2

L5 18 L4 AND L2

=> d tot ti

L5 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Memantine blocks $\alpha 7^*$ nicotinic acetylcholine receptors more potently than N-methyl-D-aspartate receptors in rat hippocampal neurons

L5 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Preparation of aryltriazoles as **glycine** transporter inhibitors.

L5 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Inhibition of nicotinic acetylcholine receptors by apolipoprotein E-derived peptides in rat hippocampal slices

L5 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Preparation of (benzyloxy)phthalimides as inhibitors of monoamine oxidase B

L5 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Chemical properties and physiological activities of synnemata of Beauveria bassiana

L5 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Transgenic animals models of Alzheimer's disease with mutant human amyloid precursor protein and screening anti-Alzheimer's agents

L5 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Preparation of 1-phenyl-1-(arylsulfonyl)cyclohexanes for treatment of Alzheimer's disease

L5 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Macrocycles useful in the treatment of alzheimer's disease

L5 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Preparation of peptide-related hydrazine derivatives for treating Alzheimer's disease

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Preparation of diaryl-ene-yne **glycine** derivatives as **glycine** transport inhibitors for treatment of schizophrenia, cognitive dysfunction, and Alzheimer's disease

L5 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Hormone replacement therapy compositions containing estradiol and an isoflavone for use in the treatment of various postmenopausal pathophysiological disorders

L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI D-cycloserine, a partial NMDA receptor-associated **glycine**-B site agonist, enhances reversal learning, but a cholinesterase inhibitor and nicotine has no effect

L5 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

TI Excitatory amino acid-induced changes in amygdaloid and hippocampal APP mRNA expression: effect of selective antagonists

L5 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN

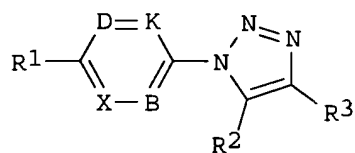
TI Time-related cortical amino acid changes after basal forebrain lesion: a

microdialysis study

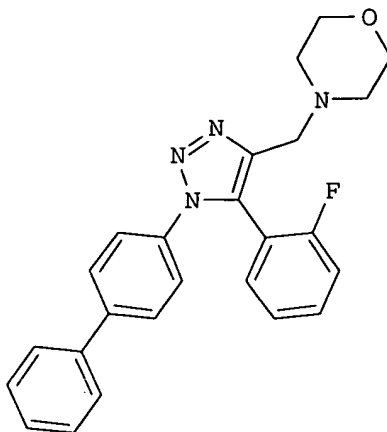
- L5 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI High-level expression and in vitro mutagenesis of a fibrillogenic 109-amino-acid C-terminal fragment of Alzheimer's-disease amyloid precursor protein
- L5 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Hyperpurification of paired helical filaments reveals elevations in hydroxyproline content and a core structure related peptide fragment
- L5 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Isolation and chemical characterization of Alzheimer's disease paired helical filament cytoskeletons: differentiation from amyloid plaque core protein
- L5 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
TI Purification, ultrastructure, and chemical analysis of Alzheimer disease amyloid plaque core protein

=> d 15 hit

- L5 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
AB The N-methyl-D-aspartate (NMDA) receptor antagonist memantine is an approved drug for treatment of Alzheimer's disease (AD). Other such treatments are cholinesterase inhibitors and nicotinic acetylcholine receptor (nAChR)-sensitizing agents such as galantamine. The present study was designed to test whether memantine exerts any effect on the cholinergic system, in particular the Ca²⁺-conducting $\alpha 7^*$ nAChR, in cultured hippocampal neurons. Memantine caused a concentration-dependent reduction of the amplitudes of whole-cell currents evoked by the $\alpha 7^*$ nAChR-selective agonist choline (10 mM) or by N-methyl-D-aspartate (NMDA) (50 μ M) plus **glycine** (10 μ M). It also inhibited tonically activated NMDA receptors. Memantine was more potent in inhibiting $\alpha 7^*$ nAChRs than NMDA receptors; at -60 mV, the IC₅₀ values for memantine were 0.34 and 5.1 μ M, resp. Consistent with an open-channel blocking mechanism, memantine-induced NMDA receptor inhibition was voltage and use-dependent; the Hill coefficient (nH) was .apprx.1. Memantine-induced $\alpha 7^*$ nAChR inhibition had an nH < 1 and showed a variable voltage dependence; the effect was voltage-independent at 0.1 μ M, becoming voltage-dependent at ≥ 1 μ M. Thus, memantine interacts with more than one class of sites on the $\alpha 7^*$ nAChRs. One is voltage-sensitive and therefore likely to be within the receptor channel. The other is voltage-insensitive and therefore likely to be in the extracellular domain of the receptor. It is suggested that blockade of $\alpha 7^*$ nAChRs by memantine could decrease its effectiveness for treatment of AD, particularly at early stages when the degrees of nAChR dysfunction and of



I



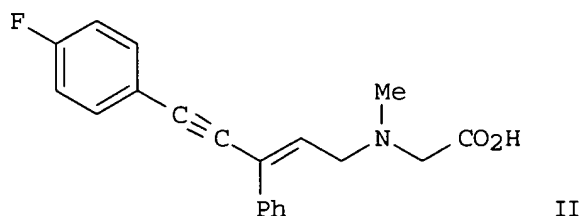
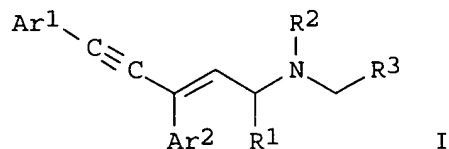
II

AB Title compds. [I; X, B, K, D = CH, N; R¹ = H, A, halo, (CH₂)_nHet, (CH₂)_nAr, cycloalkyl, CF₃, NO₂, cyano, C(NH)NOH, OCF₃; R² = (CH₂)_nHet, (CH₂)_nAr, cycloalkyl, CF₃; R³ = H, (CH₂)_nCO₂R⁵, (CH₂)_nCOHet, CHO, (CH₂)_nHet, etc.; A = alkyl, alkoxy, alkenyl, alkoxyalkyl; n = 0-5; Ar = (substituted) Ph; Het = (substituted) (unsatd.) (aromatic) mono- or bicyclic heterocyclyl, heteroatom-containing organic residue], were prepared for treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy Body Dementia, Huntington's disease, Tourette syndrome, fear, learning and memory restrictions, neurodegenerative illnesses and other cognitive impairments, as nicotine dependence, and pain (no data). Thus, title compound (II) was prepared in several steps using 4-bromophenylhydrazine hydrochloride, Et (2-fluorobenzoyl)acetate, PhB(OH)₂, and morpholine.

=> d 10 12 cbib abs

L5 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
2002:570709 Document No. 137:124979 Preparation of diaryl-enyne
glycine derivatives as **glycine** transport inhibitors for
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disease. Egle, Ian; Frey, Jennifer; Isaac, Methvin (NPS Allelix Corp.,
Can.). U.S. US 6426364 B1 20020730, 19 pp. (English). CODEN: USXXAM.
APPLICATION: US 2000-704225 20001101. PRIORITY: US 1999-PV162986
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L5 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2005 ACS on STN
1999:2158 Document No. 130:218089 D-cycloserine, a partial NMDA
receptor-associated **glycine**-B site agonist, enhances reversal
learning, but a cholinesterase inhibitor and nicotine has no effect.
Riekkinen, Paavo, Jr.; Ikonen, Sami; Riekkinen, Minna (Department of
Neurology, Canthia Building, University of Kuopio, Kuopio, FIN-70211,
Finland). NeuroReport, 9(16), 3647-3651 (English) 1998. CODEN: NERPEZ.
ISSN: 0959-4965. Publisher: Lippincott Williams & Wilkins.

AB The present study examined the efficacy of single and combined treatments
with an anticholinesterase, tetrahydroaminoacridine, nicotine and a
glycine-B site partial agonist, D-cycloserine, in alleviating the
water maze reversal learning defect induced by a medial septal lesion.
D-cycloserine (3 and 10 mg/kg) improved reversal learning.
Tetrahydroaminoacridine (1 and 3 mg/kg) and nicotine (0.1 and 0.3 mg/kg)
had no effect on reversal learning. A combination of

tetrahydroaminoacridine 3 mg/kg or nicotine 0.3 mg/kg and D-cycloserine 10 mg/kg was not more effective than D-cycloserine 10 mg/kg alone in improving reversal learning. This suggests that stimulation of NMDA mechanisms may more effectively improve in medial septal-lesioned rats reversal learning processes than stimulation of cholinergic activity. The data support the development and testing of compounds that may enhance NMDA receptor activation for use in the treatment of Alzheimer's disease.

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